

WHAT IS CLAIMED IS:

1. A method of screening for modulators of IKK and JNK activation comprising:
 - 5 (a) providing a Ubc13/Uev1A complex and TRAF6 or TRAF2;
 - (b) contacting said complex and TRAF6 or TRAF2 with a candidate modulator substance in the presence of E1, a plurality of ubiquitin molecules and ATP;
 - (c) determining the formation of free polyubiquitin chains,
10 wherein a change in poly-ubiquitin formation in the presence of said candidate modulator, as compared with poly-ubiquitin formation in the absence of said candidate modulator, indicates that said candidate modulator is an modulator of IKK and JNK activation.
2. The method of claim 1, further comprising measuring poly-ubiquitin formation in
15 the absence of said candidate modulator.
3. The method of claim 1, wherein said candidate modulator is a protein or peptide.
4. The method of claim 1, wherein said candidate modulator is an expression construct.
5. The method of claim 1, wherein candidate modulator is an organic small
20 molecule.
6. The method of claim 1, wherein said candidate modulator is an inhibitor.
7. The method of claim 1, wherein said candidate modulator is a stimulator.
8. The method of claim 1, wherein candidate modulator is an inorganic small
molecule.

9. The method of claim 1, wherein candidate modulator is a DNA oligonucleotide or its analogue.
10. The method of claim 1, wherein candidate modulator is an RNA oligonucleotide or its analogue.
- 5 11. The method of claim 2, further comprising measuring poly-ubiquitin formation by immunodetection.
12. The method of claim 11, wherein immunodetection comprises detecting ubiquitin fused to an immunodetectable marker.
13. The method of claim 13, wherein said immunodetectable marker is myc or His6X.
- 10 14. The method of claim 11, wherein the format of the immunodetection is ELISA.
15. The method of claim 2, wherein the plurality of ubiquitin molecules comprise a single lysine residue at position 63.
16. A method of screening for modulators of IKK and JNK activation comprising:
(a) providing a Ubc13/Uev1A complex, TRAF6 or TRAF2;
15 (b) contacting TAB1/TAB2/TAK1 complex, Ubc13/Uev1A complex, TRAF6 or TRAF2 with a candidate modulator substance in the presence of E1, a plurality of ubiquitin molecules and ATP;
(c) determining the polyubiquitination of TRAF6 or TRAF2,
wherein a change in the phosphorylation state of IKK or MKK in the presence of
20 said candidate modulator, as compared with the phosphorylation state of IKK or MKK in the absence of said candidate modulator, indicates that said candidate modulator is an modulator of IKK and JNK activation.

17. The method of claim 16, further comprising measuring the polyubiquitination state of TRAF6 or TRAF2 in the absence of said candidate modulator.
18. The method of claim 16, wherein said candidate modulator is a protein or peptide.
19. The method of claim 16, wherein said candidate modulator is an expression construct.
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20. The method of claim 16, wherein candidate modulator is an organic small molecule.
21. The method of claim 16, wherein said candidate modulator is an inhibitor.
22. The method of claim 16, wherein said candidate modulator is a stimulator.
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- The method of claim 16, wherein candidate modulator is an inorganic small molecule.
23. The method of claim 16, wherein candidate modulator is a DNA oligonucleotide or its analogue.
24. The method of claim 16, wherein candidate modulator is an RNA oligonucleotide or its analogue.
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25. The method of claim 17, further comprising measuring poly-ubiquitin state of TRAF6 or TRAF2 by immunodetection.
26. The method of claim 25, wherein immunodetection comprises detecting TRAF2, TRAF6 or ubiquitin fused to an immunodetectable marker.
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27. The method of claim 26, wherein said ubiquitin molecule comprises a single lysine residue at position 63.
28. The method of claim 26, wherein said immunodetectable marker is 6HisX or myc.
29. The method of claim 25, wherein the format of said immunodetection is ELISA.

30. A method of screening for modulators of IKK and JNK activation comprising:
- (a) providing a TRAF2 or a TRAF6;
 - (b) contacting TRAF2 or TRAF6 with a candidate modulator substance in the presence of E1, Ubc13/Uev1A, a plurality of ubiquitin molecules and ATP;
 - (c) determining the ubiquitin ligase activity of TRAF2 or TRAF6,
- wherein a change in the enzyme activity of TRAF2 or TRAF6 in the presence of said candidate modulator, as compared with the activity of TRAF2 or TRAF6 in the absence of said candidate modulator, indicates that said candidate modulator is an modulator of IKK and JNK activation.
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31. The method of claim 30, further comprising measuring TRAF2 or TRAF6 activity in the absence of said candidate modulator.
32. The method of claim 30, wherein said candidate modulator is a protein or peptide.
33. The method of claim 30, wherein said candidate modulator is an expression construct.
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34. The method of claim 30, wherein candidate modulator is an organic or inorganic small molecule.
35. The method of claim 30, wherein said candidate modulator is an inhibitor.
36. The method of claim 30, wherein said candidate modulator is a stimulator.
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37. The method of claim 30, wherein candidate modulator is a DNA oligonucleotide or its analogue.
38. The method of claim 30, wherein candidate modulator is an RNA oligonucleotide or its analogue.

39. The method of claim 30, further comprising measuring poly-ubiquitin formation by immunodetection.
40. The method of claim 39, wherein immunodetection comprises detecting ubiquitin fused to an immunodetectable marker.
- 5 41. The method of claim 40, wherein said immunodetectable marker is myc or His6X.
42. A method of screening for modulators of IKK and JNK activation comprising:
- (a) providing TAK1, TAB1, TRAF6 and TAB2;
- (b) contacting TAK1, TAB1, TRAF6 and TAB2 with a candidate modulator substance in the presence of E1, Ubc13/Uev1A, a plurality of ubiquitin molecules and ATP;
- 10 (c) determining the kinase activity of TAK 1,
- wherein a change in the kinase activity of TAK1 in the presence of said candidate modulator, as compared with the kinase activity of TAK1 in the absence of said candidate modulator, indicates that said candidate modulator is an modulator of IKK and JNK activation.
- 15 43. The method of claim 42, further comprising measuring TAK1 activity in the absence of said candidate modulator.
44. The method of claim 42, wherein said candidate modulator is a protein or peptide.
45. The method of claim 42, wherein said candidate modulator is an expression construct.
- 20 46. The method of claim 42, wherein candidate modulator is an organic small molecule.
47. The method of claim 42, wherein said candidate modulator is an inhibitor.

48. The method of claim 42, wherein said candidate modulator is a stimulator.
- The method of claim 42, wherein candidate modulator is an inorganic small molecule.
49. The method of claim 42, wherein candidate modulator is a DNA oligonucleotide or its analogue.
50. The method of claim 42, wherein candidate modulator is an RNA oligonucleotide or its analogue.
51. The method of claim 42, wherein TAK1 kinase activity is measured by determining the phosphorylation state of I κ B α incubated with said TAK1.
- 10 52. The method of claim 51, wherein said phosphorylation state is determined with an antibody that binds selectively to phosphorylated I κ B α .
53. The method of claim 52, wherein the format of the assay is ELISA.
54. A method of screening for modulators of IKK and JNK activation comprising:
- 15 (a) providing TAK1, TAB1, TAB2, TRAF6 and IKK complex;
- (b) contacting TAK1, TAB1, TAB2, TRAF6 and IKK complex with a candidate modulator substance in the presence of E1, Ubc13/Uev1A, a plurality of ubiquitin molecules and ATP;
- (c) determining the phosphorylation state of I κ B and MKK,
- wherein a change in the phosphorylation state of I κ B and MKK in the presence of said candidate modulator, as compared with the phosphorylation state of I κ B and MKK in the absence of said candidate modulator, indicates that said candidate modulator is an modulator of IKK and JNK activation.

55. The method of claim 54, further comprising measuring the phosphorylation of I_KB α or MKK in the absence of said candidate modulator.
56. The method of claim 54, wherein said candidate modulator is a protein or peptide.
57. The method of claim 54, wherein said candidate modulator is an expression construct.
58. The method of claim 54, wherein candidate modulator is an organic small molecule.
59. The method of claim 54, wherein said candidate modulator is an inhibitor.
60. The method of claim 54, wherein said candidate modulator is a stimulator.
- 10 61. The method of claim 54, wherein candidate modulator is an inorganic small molecule.
62. The method of claim 54, wherein candidate modulator is a DNA oligonucleotide or its analogue.
- 15 63. The method of claim 54, wherein said phosphorylation state of I_KB α is determined with an antibody that binds selectively to phosphorylated I_KB α .
64. The method of claim 54, wherein said phosphorylation state of MKK is determined with an antibody that binds selectively to phosphorylated MKK.
- 20 65. The method of claim 54, wherein the format of the assay is ELISA.
66. The method of claim 55, wherein the format of the assay is ELISA.